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Beyond a positive label: Treatment-specific biomarkers for targeted cancer therapy

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A target-positive result can establish treatment eligibility without identifying the preferred regimen. As therapeutic options expand around shared targets, biomarker development must address treatment choice as well as eligibility. The problem is not binary classification itself, but transferring a biomarker between drugs or combinations without validating its role in the new setting. Treatment-specific biomarkers should answer a defined question: which patients obtain sufficient additional benefit from one regimen over another?

The August 2026 US Food and Drug Administration (FDA) approvals illustrate this distinction. Zanidatamab-based regimens were approved for first-line treatment of adults with unresectable locally advanced or metastatic human epidermal growth factor receptor 2 (HER2)-positive gastric, gastroesophageal junction or esophageal adenocarcinoma. Eligibility, established using an FDA-approved test, differs by regimen: immunohistochemistry (IHC) 3+ for zanidatamab plus fluoropyrimidine–platinum chemotherapy; IHC 3+ or IHC 2+/in situ hybridization (ISH)-positive status when tislelizumab is included.[1] Tislelizumab targets programmed death 1 (PD-1), blocking the receptor's interaction with its ligands, including programmed death ligand 1 (PD-L1).[2] These regimen-specific criteria reflect trial evidence and regulatory decisions; their difference alone does not establish a treatment-selection biomarker or show that PD-1 blockade lowers the antigen requirement. For patients with IHC 3+ disease eligible for both regimens, who benefits sufficiently from adding tislelizumab?

DEFINING THE TREATMENT COMPARISON

HERIZON-GEA-01 randomized 914 patients to zanidatamab plus chemotherapy, zanidatamab plus tislelizumab and chemotherapy, or trastuzumab plus chemotherapy. At the 1 October 2025 data cutoff reported in the primary publication, median progression-free survival was 12.4 months with either zanidatamab regimen versus 8.1 months with the control regimen. At the first interim overall survival analysis, the tislelizumab-containing regimen improved median survival to 26.4 months versus 19.2 months (hazard ratio for death, 0.72; 95% confidence interval, 0.57–0.90).[2]

HERIZON-GEA-01 included zanidatamab plus chemotherapy with and without tislelizumab, but the confirmatory comparisons reported in the primary publication evaluated each regimen against trastuzumab plus chemotherapy.[2] These comparisons do not, by themselves, identify which patients gain additional benefit from adding tislelizumab. To guide this choice, biomarker analyses should compare outcomes with versus without tislelizumab on the same zanidatamab–chemotherapy backbone and assess whether the incremental benefit varies with biomarker status.

PD-L1 expression was assessed retrospectively using a tumor area positivity score rather than a combined positive score. Subgroup confidence intervals were not adjusted for multiplicity, and no pembrolizumab-containing comparator was included.[2] Assay and comparator differences constrain subsequent treatment-selection claims.

IDENTIFYING TREATMENT-RELEVANT BIOLOGY

Once the comparison is defined, candidate measurements should reflect the treatments' pharmacology. Zanidatamab binds two extracellular HER2 domains; preclinical studies support receptor clustering, internalization and degradation, alongside complement- and Fc-mediated cytotoxicity.[2] Antibody–drug conjugates (ADCs) use antigen recognition to deliver cytotoxic

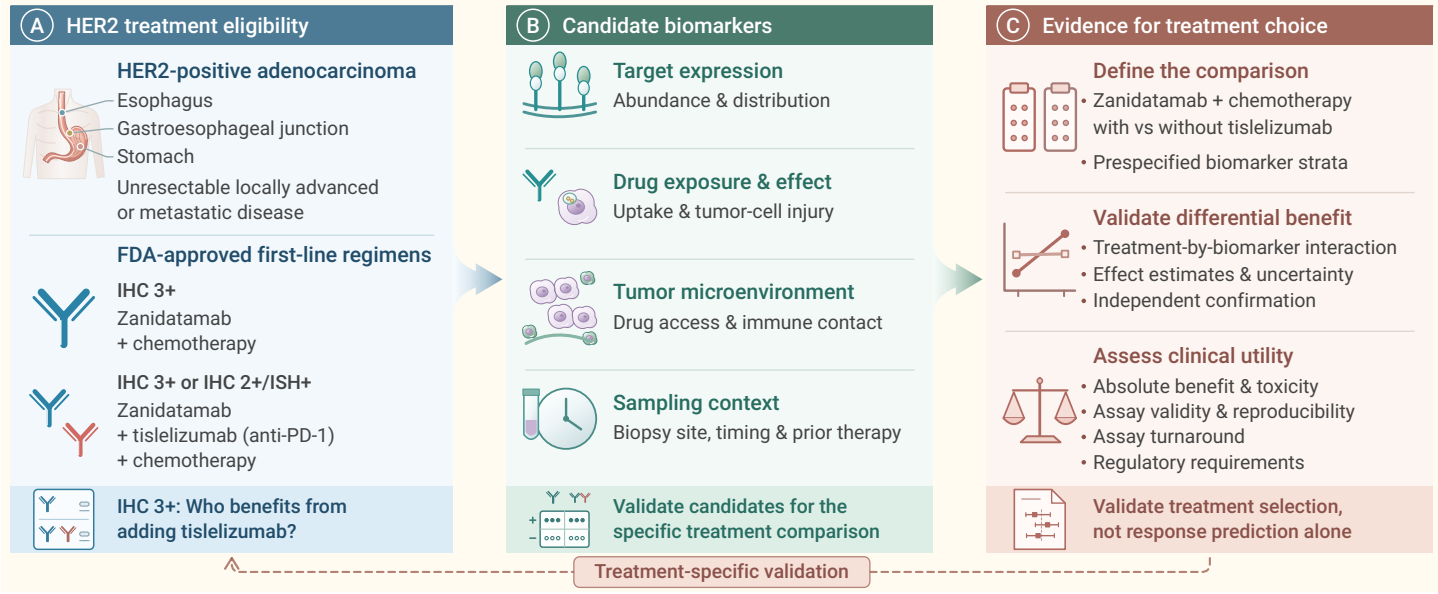


Figure 1. From HER2 treatment eligibility to treatment-specific biomarker validation (A) Approved first-line zanidatamab regimens have different HER2 criteria; IHC 3+ disease meets both, raising the question of benefit from adding the anti-PD-1 antibody tislelizumab.[1] (B) Target expression, drug exposure and effect, tumor microenvironment and sampling context guide candidate measurements, not validated treatment-selection rules. (C) Prespecified treatment comparisons and treatment-by-biomarker interaction analyses assess differential benefit through effect estimates, uncertainty and independent confirmation.[5] Clinical utility and implementation additionally require evaluation of absolute benefit, toxicity, assay validity, reproducibility, turnaround and applicable regulatory requirements. Arrows indicate a proposed evidence framework, not a prescribing algorithm; the dashed return arrow emphasizes treatment-specific validation. Chemotherapy denotes fluoropyrimidine–platinum treatment. FDA, Food and Drug Administration; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; PD-1, programmed death 1.

payloads, making intracellular processing and payload susceptibility additional determinants of activity.[3] These mechanisms overlap, but target abundance, signaling dependence and treatment susceptibility remain distinct. More precise expression measurement does not necessarily identify the step limiting efficacy.

SYS6010 illustrates this distinction. In a single-arm phase 1 study, this epidermal growth factor receptor (EGFR)-directed ADC showed activity in previously treated EGFR-mutant and wild-type non-small cell lung cancer.[3] Exploratory expression analyses used IHC 3+ staining in at least 10% of tumor cells, with the threshold derived from a preliminary post hoc analysis. These findings generate sensitivity hypotheses, but cannot establish that expression modifies benefit relative to another treatment. A selection or exclusion threshold requires independent clinical validation.

SELECTING CANDIDATE BIOMARKERS

Biomarker development should retain validated target testing and add measurements linked to the pharmacology of the proposed treatment (Figure 1). For ADCs, these may distinguish antigen availability, drug distribution, intracellular processing and cytotoxic injury. For immune-mediated regimens, the question is whether target recognition is accompanied by productive immune contact and activation. Drug properties guide which patient-level measurements are relevant; they are not themselves patient biomarkers. These measurements remain candidates, not established selection rules.

Spatial studies can test whether similarly expressing tumors differ in drug access or immune cell contact. Linking baseline architecture to on-treatment pharmacology and outcome, with perturbation experiments where feasible, would distinguish proposed barriers from descriptive associations. Stromal abundance alone cannot establish the cause of treatment failure, nor can proximity establish productive immune killing.

Beyond HER2 and ADCs, Chen et al. identified an IGF2BP2–CEMIP pathway linking colorectal cancer cells to endothelial activation. Inhibiting IGF2BP2 enhanced antiangiogenic treatment in mouse models. An exploratory analysis of human data also associated IGF2BP2 expression with bevacizumab response.[4] These preclinical and correlative findings nominate a pathway for biomarker development, not a clinically validated rule for choosing between regimens. A target for improving treatment is not automatically a marker for selecting it.

Sampling context also matters. SYS6010 analyses relied primarily on archival tissue.[3] A specimen collected before intervening therapy may not represent the tumor at the next treatment decision. Studies should document biopsy site, timing and prior treatment; repeat sampling should be justified by its likely clinical value, feasibility and risks.

CLINICAL VALIDATION AND IMPLEMENTATION

A prognostic biomarker informs outcome risk in a specified clinical context without necessarily indicating which treatment is preferable. A predictive biomarker identifies variation in treatment effect for a defined intervention–comparator pair. A marker may have both roles. Association with outcome in a treated-only cohort does not establish differential treatment benefit.[5]

Differential effects should be assessed through prespecified treatment-by-biomarker interaction testing on an explicit effect scale, with effect estimates and confidence intervals. Significance in one biomarker subgroup but not another does not establish an interaction. Conversely, a non-significant interaction in a small study does not demonstrate identical effects. Power and multiplicity require attention when several candidate interactions are evaluated.

The immediate priority is to embed biomarker evaluation in trials addressing an actual treatment choice. Where feasible and clinical equipoise remains, randomized phase 2 studies could compare a common backbone with and without an added agent across prespecified biomarker strata, in patients eligible for both regimens. For zanidatamab, the question concerns adding tislelizumab in IHC 3+ disease. Assays, biomarker modeling, any cutoffs and interaction analyses should be specified prospectively; continuous markers need not be dichotomized. Estimates from small early-phase studies remain exploratory and require adequately powered confirmation.

Existing trial collections offer a complementary route. Prospective–retrospective studies require assays analytically and preanalytically validated for archived tissue, a classifier and analysis plan locked before testing, representative specimens sufficient for adequately powered analyses, assays blinded to clinical data, and confirmation in a similarly designed independent study.[5] These safeguards allow archived tissue to address a defined therapeutic question.

Validation must also address clinical utility. In HERIZON-GEA-01, grade 3 or higher adverse events of any cause occurred in 83.3% of patients receiving zanidatamab, tislelizumab and chemotherapy, versus 73.8% with zanidatamab and chemotherapy.[2] These descriptive, non-exposure-adjusted rates are not estimates of toxicity attributable solely to tislelizumab. Studies should estimate absolute benefit and weigh toxicity and treatment burden. Baseline risk can produce different absolute benefits despite similar relative effects, potentially changing a decision without establishing drug-specific sensitivity. Conversely, a predictive marker may add little if the preferred regimen remains unchanged. An inadequately validated negative result could deny effective therapy.

Implementation requires standardized specimen handling, analytical validation of accuracy and precision, inter-laboratory concordance and prespecified scoring rules. Assay turnaround must fit the treatment decision. Developers should anticipate applicable regulatory requirements for companion diagnostics and their intended use, including the link to the specified therapeutic product. Tissue requirements, complexity and cost are justified only by clinical value beyond existing assessment.

Measurements may be reusable when drugs share relevant mechanisms, but interpretation requires reassessment when the payload, combination partner or treatment line changes. Treatment specificity should define where a test remains reliable, rather than fragment testing unnecessarily.

Target detection remains essential for treatment eligibility. The next step is to determine when additional measurements distinguish the benefits and harms of available regimens. A treatment-specific biomarker earns clinical value by improving a defined choice, rather than creating another category of positive patients.

DECLARATION OF GENERATIVE AI AND AI-ASSISTED TECHNOLOGIES IN THE WRITING PROCESS

Tencent WorkBuddy was used for manuscript formatting, layout preparation, and editing of ancillary sections. The author reviewed and edited the output and takes full responsibility for the publication.

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DECLARATION OF INTERESTS

The author declares no competing interests.